WHAT IS CLAIMED:

1. The peptide comprising an amino acid sequence with at least 90% identity to SEQ ID NO:7.

2. A peptide comprising SEQ ID NO:5 or SEQ ID NO:7.

3. An inhibitor of hypoxia-inducible factor 1 alpha ubiquitination comprising a peptide of formula I or II:

Xaa_1-Xaa_2-Xaa_3-Xaa_4-Xaa_5-Xaa_6-Xaa_7-Xaa_8-Xaa_9-Xaa_{10}-Xaa_{11}-Xaa_{12}-Xaa_{13}-Xaa_{14}-Xaa_{15}-Xaa_{16}-Xaa_{17}-Xaa_{18}-Xaa_{19} (I)

Xaa_7-Xaa_8-Xaa_9-Xaa_{10}-Xaa_{11}-Xaa_{12} Xaa_{13}-Xaa_{14} (II)

wherein

Xaa_1, Xaa_3, Xaa_5, Xaa_{14}, Xaa_{15} and Xaa_{16} are each a separate acidic amino acid;

Xaa_2, Xaa_4, Xaa_7, Xaa_8, Xaa_{11} and Xaa_{19} are each a separate aliphatic amino acids;

Xaa_6, Xaa_{10} and Xaa_{18} are each a separate polar amino acid;

Xaa_9 is hydroxyproline;

Xaa_{12} and Xaa_{13} are separately an apolar amino acid such as methionine, glycine or proline; and

Xaa_{17} is an aromatic amino acid such as phenylalanine, tyrosine, tryptophan, phenylglycine, naphthylalanine, β-2-thienylalanine, 1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid, 4-chlorophenylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, pyridylalanine, or 3-benzothienyl alanine.

4. The inhibitor of claim 3 wherein the acidic amino acid is aspartic acid or glutamic acid.

5. The inhibitor of claim 3 wherein the aliphatic amino acid is alanine, valine, leucine, isoleucine, t-butylalanine, t-butylalanine, N–methylisoleucine, norleucine, N-methylvaline, cyclohexylalanine, β-alanine, N-methylglycine, or α-aminoisobutyric acid.

6. The inhibitor of claim 3 wherein the polar amino acid is asparagine, glutamine, serine, threonine, tyrosine, citrulline, N-acetyl lysine, methionine sulfoxide, or homoserine.

7. The inhibitor of claim 3 wherein the apolar amino acid is methionine, glycine or proline.

8. The inhibitor of claim 3 wherein the aromatic amino is phenylalanine, tyrosine, tryptophan, phenylglycine, naphthylalanine, β-2-thienylalanine, 1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid, 4-chlorophenylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, pyridylalanine, or 3-benzothienyl alanine.

9. The inhibitor of claim 3 wherein the peptide comprises an amino acid sequence with at least 90% identity to SEQ ID NO:4, SEQ ID NO:5 or SEQ ID NO:7.

10. The inhibitor of claim 3 wherein the peptide has an amino acid sequence comprising SEQ ID NO:4, SEQ ID NO:5 or SEQ ID NO:7.

11. An activator of VEGF transcription comprising a peptide of formula I or II:

Xaa_1-Xaa_2-Xaa_3-Xaa_4-Xaa_5-Xaa_6-Xaa_7-Xaa_8-Xaa_9-Xaa_{10}-Xaa_{11}-
Xaa_{12}-Xaa_{13}-Xaa_{14}-Xaa_{15}-Xaa_{16}-Xaa_{17}-Xaa_{18}-Xaa_{19} (I)

Xaa_7-Xaa_8-Xaa_9-Xaa_{10}-Xaa_{11}-Xaa_{12} Xaa_{13}-Xaa_{14} (II)

wherein

Xaa_1, Xaa_3, Xaa_5, Xaa_{14}, Xaa_{15} and Xaa_{16} are each a separate acidic amino acid;

Xaa_2, Xaa_4, Xaa_7, Xaa_8, Xaa_{11} and Xaa_{19} are each a separate aliphatic amino acids;

Xaa_6, Xaa_{10} and Xaa_{18} are each a separate polar amino acid;

Xaa_9 is hydroxyproline;

Xaa_{12} and Xaa_{13} are separately an apolar amino acid such as methionine, glycine or proline; and

Xaa_{17} is an aromatic amino acid such as phenylalanine, tyrosine, tryptophan, phenylglycine, naphthylalanine, β-2-thienylalanine, 1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid, 4-chlorophenylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, pyridylalanine, or 3-benzothienyl alanine.

12. The activator of claim 11 wherein the acidic amino acid is aspartic acid or glutamic acid.

13. The activator of claim 11 wherein the aliphatic amino acid is alanine, valine, leucine, isoleucine, t-butylalanine, t-butylalanine, N–methylisoleucine, norleucine, N-methylvaline, cyclohexylalanine, β-alanine, N-methylglycine, or α-aminoisobutyric acid.

14. The activator of claim 11 wherein the polar amino acid is asparagine, glutamine, serine, threonine, tyrosine, citrulline, N-acetyl lysine, methionine sulfoxide, or homoserine.

15. The activator of claim 11 wherein the apolar amino acid is methionine, glycine or proline.

16. The activator of claim 11 wherein the aromatic amino is phenylalanine, tyrosine, tryptophan, phenylglycine, naphthylalanine, β-2-thienylalanine,

1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid, 4-chlorophenylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, pyridylalanine, or 3-benzothienyl alanine.

17. The activator of claim 11 wherein the peptide comprises an amino acid sequence with at least 90% identity to SEQ ID NO:4, SEQ ID NO:5 or SEQ ID NO:7.

18. The activator of claim 11 wherein the peptide has an amino acid sequence comprising SEQ ID NO:4, SEQ ID NO:5 or SEQ ID NO:7.

19. A pharmaceutical formulation comprising a peptide of formula I or II and a pharmaceutically acceptable carrier:

Xaa_1-Xaa_2-Xaa_3-Xaa_4-Xaa_5-Xaa_6-Xaa_7-Xaa_8-Xaa_9-Xaa_{10}-Xaa_{11}-
Xaa_{12}-Xaa_{13}-Xaa_{14}-Xaa_{15}-Xaa_{16}-Xaa_{17}-Xaa_{18}-Xaa_{19} (I)

Xaa_7-Xaa_8-Xaa_9-Xaa_{10}-Xaa_{11}-Xaa_{12} Xaa_{13}-Xaa_{14} (II)

wherein

Xaa_1, Xaa_3, Xaa_5, Xaa_{14}, Xaa_{15} and Xaa_{16} are each a separate acidic amino acid;

Xaa_2, Xaa_4, Xaa_7, Xaa_8, Xaa_{11} and Xaa_{19} are each a separate aliphatic amino acids;

Xaa_6, Xaa_{10} and Xaa_{18} are each a separate polar amino acid;

Xaa_9 is hydroxyproline;

Xaa_{12} and Xaa_{13} are separately an apolar amino acid such as methionine, glycine or proline; and

Xaa_{17} is an aromatic amino acid such as phenylalanine, tyrosine, tryptophan, phenylglycine, naphthylalanine, β-2-thienylalanine, 1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid, 4-chlorophenylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, pyridylalanine, or 3-benzothienyl alanine.

20. The pharmaceutical formulation of claim 19 wherein the acidic amino acid is aspartic acid or glutamic acid.

21. The pharmaceutical formulation of claim 19 wherein the aliphatic amino acid is alanine, valine, leucine, isoleucine, t-butylalanine, t-butylalanine, N–methylisoleucine, norleucine, N-methylvaline, cyclohexylalanine, β-alanine, N-methylglycine, or α-aminoisobutyric acid.

22. The pharmaceutical formulation of claim 19 wherein the polar amino acid is asparagine, glutamine, serine, threonine, tyrosine, citrulline, N-acetyl lysine, methionine sulfoxide, or homoserine.

23. The pharmaceutical formulation of claim 19 wherein the apolar amino acid is methionine, glycine or proline.

24. The pharmaceutical formulation of claim 19 wherein the aromatic amino is phenylalanine, tyrosine, tryptophan, phenylglycine, naphthylalanine, β-2-thienylalanine, 1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid, 4-chlorophenylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, pyridylalanine, or 3-benzothienyl alanine.

25. The pharmaceutical formulation of claim 19 wherein the peptide comprises an amino acid sequence with at least 90% identity to SEQ ID NO:4, SEQ ID NO:5 or SEQ ID NO:7.

26. The pharmaceutical formulation of claim 19 wherein the peptide has an amino acid sequence comprising SEQ ID NO:4, SEQ ID NO:5 or SEQ ID NO:7.

27. The pharmaceutical formulation of claim 19 that is a wound dressing.

28. The pharmaceutical formulation of claim 19 that is a sustained release formulation.

29. The pharmaceutical formulation of claim 19 that is a surgical implant.

30. A method of inhibiting hypoxia-inducible factor 1 alpha ubiquitination in a mammalian cell comprising contacting a mammalian cell with a peptide of formula I or II:

Xaa_1-Xaa_2-Xaa_3-Xaa_4-Xaa_5-Xaa_6-Xaa_7-Xaa_8-Xaa_9-Xaa_{10}-Xaa_{11}-
Xaa_{12}-Xaa_{13}-Xaa_{14}-Xaa_{15}-Xaa_{16}-Xaa_{17}-Xaa_{18}-Xaa_{19} (I)

Xaa_7-Xaa_8-Xaa_9-Xaa_{10}-Xaa_{11}-Xaa_{12} Xaa_{13}-Xaa_{14} (II)

wherein

Xaa_1, Xaa_3, Xaa_5, Xaa_{14}, Xaa_{15} and Xaa_{16} are each a separate acidic amino acid;

Xaa_2, Xaa_4, Xaa_7, Xaa_8, Xaa_{11} and Xaa_{19} are each a separate aliphatic amino acids;

Xaa_6, Xaa_{10} and Xaa_{18} are each a separate polar amino acid;

Xaa_9 is hydroxyproline;

Xaa_{12} and Xaa_{13} are separately an apolar amino acid such as methionine, glycine or proline; and

Xaa_{17} is an aromatic amino acid such as phenylalanine, tyrosine, tryptophan, phenylglycine, naphthylalanine, β-2-thienylalanine, 1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid, 4-chlorophenylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, pyridylalanine, or 3-benzothienyl alanine.

31. The method of claim 30 wherein the acidic amino acid is aspartic acid or glutamic acid.

32. The method of claim 30 wherein the aliphatic amino acid is alanine, valine, leucine, isoleucine, t-butylalanine, t-butylalanine, N–methylisoleucine, norleucine, N-methylvaline, cyclohexylalanine, β-alanine, N-methylglycine, or α-aminoisobutyric acid.

33. The method of claim 30 wherein the polar amino acid is asparagine, glutamine, serine, threonine, tyrosine, citrulline, N-acetyl lysine, methionine sulfoxide, or homoserine.

34. The method of claim 30 wherein the apolar amino acid is methionine, glycine or proline.

35. The method of claim 30 wherein the aromatic amino is phenylalanine, tyrosine, tryptophan, phenylglycine, naphthylalanine, β-2-thienylalanine, 1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid, 4-chlorophenylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, pyridylalanine, or 3-benzothienyl alanine.

36. The method of claim 30 wherein the peptide comprises an amino acid sequence with at least 90% identity to SEQ ID NO:4, SEQ ID NO:5 or SEQ ID NO:7.

37. The method of claim 30 wherein the peptide has an amino acid sequence comprising SEQ ID NO:4, SEQ ID NO:5 or SEQ ID NO:7.

38. The method of claim 30 wherein the mammalian cell is a human cell and the method is performed in vivo.

39. The method of claim 30 wherein the method is performed in vitro.

40. A method of activating VEGF transcription in a mammalian cell comprising contacting a mammalian cell with a peptide of formula I or II:

Xaa_1-Xaa_2-Xaa_3-Xaa_4-Xaa_5-Xaa_6-Xaa_7-Xaa_8-Xaa_9-Xaa_{10}-Xaa_{11}-
Xaa_{12}-Xaa_{13}-Xaa_{14}-Xaa_{15}-Xaa_{16}-Xaa_{17}-Xaa_{18}-Xaa_{19} (I)

Xaa_7-Xaa_8-Xaa_9-Xaa_{10}-Xaa_{11}-Xaa_{12} Xaa_{13}-Xaa_{14} (II)

wherein

Xaa_1, Xaa_3, Xaa_5, Xaa_{14}, Xaa_{15} and Xaa_{16} are each a separate acidic amino acid;

Xaa_2, Xaa_4, Xaa_7, Xaa_8, Xaa_{11} and Xaa_{19} are each a separate aliphatic amino acids;

Xaa_6, Xaa_{10} and Xaa_{18} are each a separate polar amino acid;

Xaa_9 is hydroxyproline;

Xaa_{12} and Xaa_{13} are separately an apolar amino acid such as methionine, glycine or proline; and

Xaa_{17} is an aromatic amino acid such as phenylalanine, tyrosine, tryptophan, phenylglycine, naphthylalanine, β-2-thienylalanine, 1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid, 4-chlorophenylalanine, 2-fluorophenylalanine, 3-fluorophenylalanine, 4-fluorophenylalanine, pyridylalanine, or 3-benzothienyl alanine.

41. The method of claim 40 wherein the acidic amino acid is aspartic acid or glutamic acid.

42. The method of claim 40 wherein the aliphatic amino acid is alanine, valine, leucine, isoleucine, t-butylalanine, t-butylalanine, N–methylisoleucine, norleucine, N-methylvaline, cyclohexylalanine, β-alanine, N-methylglycine, or α-aminoisobutyric acid.

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Abstract

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ABSTRACT

The invention provides peptide inhibitors that inhibit ubiquitination of hypoxia inducible factor 1 alpha (HIP 1-α) and thereby activate transcription of erythropoietin (EPO), vascular endothelial growth factor (VEGF), and certain glycolytic enzymes. The invention further provides formulations containing the present peptides and methods of using the present peptides for therapeutic purposes. Such therapeutic purposes include stimulating angiogenesis in injured tissues such as chronic wounds, heart tissues injured by ischemia or heart attack, and neural tissues injured by stroke.